

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

- a pharmaceutically acceptable excipient, diluent or carrier;
- a therapeutically effective amount of at least one estrogen or prodrug thereof; and
- 5 a therapeutically effective amount of at least one selective estrogen receptor modulator or prodrug thereof, wherein said modulator is a different compound from said estrogen and said modulator is not a benzothiophene derivative, a phenylindole derivative, a naphthalene derivative, an isoquinoline derivative or an enantiomeric mixture of 3-phenylquinoline derivatives, 3-phenylthiochroman derivatives, and 3-phenylchroman derivatives having more than 10 % of the enantiomer of 2R configuration.

2. A pharmaceutical composition comprising:

- a pharmaceutically acceptable excipient, diluent or carrier;
- b) a therapeutically effective amount of at least one estrogen or prodrug thereof;
- 5 (c) a therapeutically effective amount of at least one selective estrogen receptor modulator or prodrug thereof, wherein said modulator is a different compound from said estrogen; and
- (d) a therapeutically effective amount of at least one additional agent selected from the group consisting of bisphosphonate, progestogen, an androgenic agent, testosterone, dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol, 4-androstene-3,17-dione, and a prodrug of any of the foregoing additional agents.

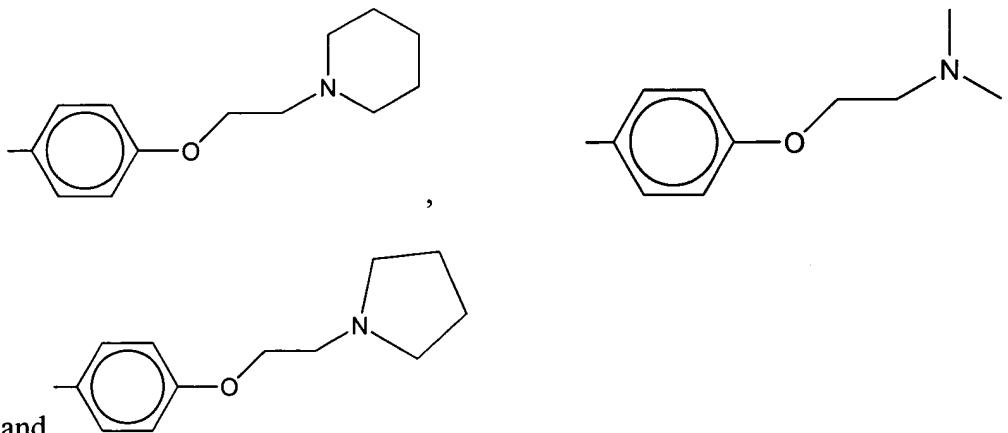
10 3. The pharmaceutical composition of claim 1, wherein the selective estrogen receptor modulator has a molecular formula with the following features:

5 a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or substituted by a hydroxyl group or a group converted in vivo to hydroxyl;

b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof;

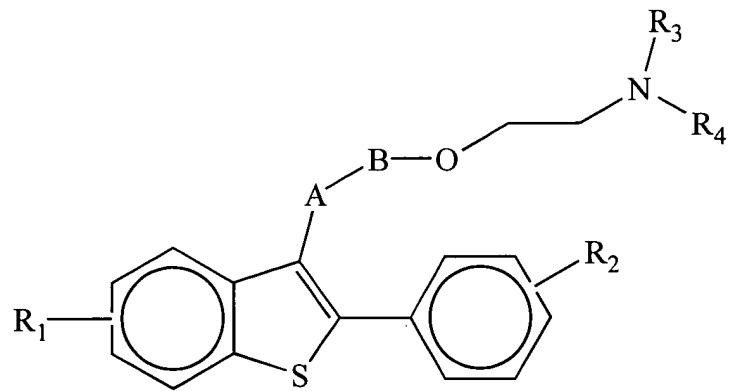
10 and wherein said modulator is not a benzothiophene derivative, a phenylindole derivative, a naphthalene derivative, an isoquinoline derivative or an enantiomeric mixture of 3-phenylquinoline derivatives, 3-pheynulthiochroman derivatives, and 3-phenylchroman derivatives having more than 10% of the enantiomer of 2R configuration.

4. The pharmaceutical composition of claim 3, wherein the side chain is selected from the group consisting of:



5. The pharmaceutical composition of claim 3, wherein the selective estrogen receptor modulator is selected from the group consisting of a triphenylethylene derivative, benzopyran derivative, HMR 3339, HMR 3656, LY 335124, LY 326315, SH 646, ERA 923 and centchroman derivative.

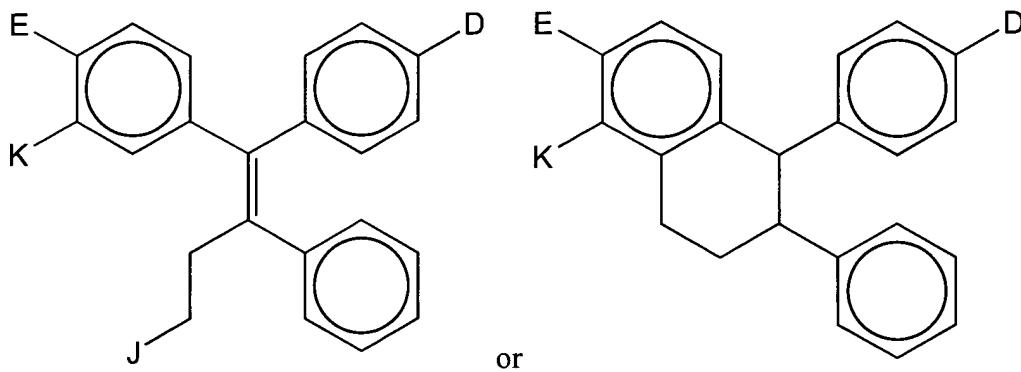
6. The pharmaceutical composition of claim 2, wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:



5 wherein R₁ and R₂ are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl ;
wherein R₃ and R₄ are either (a) independently C1-C4 alkyl, or (b) a moiety which in combination with the nitrogen to which they are bound, is selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;
10 wherein A is selected from the group consisting of -CO-, -CHOH, and -CH₂-;
wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC₄H₂N₂-.

7. The pharmaceutical composition of claim 6, wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

8. The pharmaceutical composition of claim 3, wherein the selective estrogen receptor modulator is a triphenylethylene or diphenylhydronaphthalene derivative compound of the following formula:

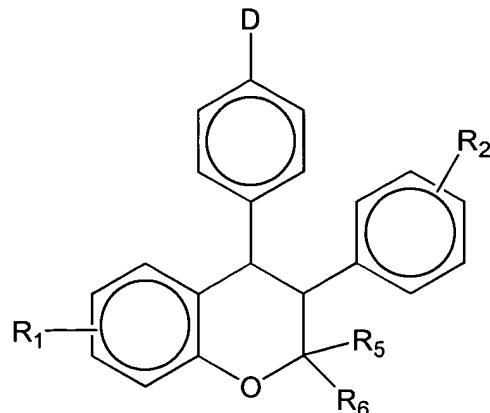


5 wherein D is $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$, $-\text{OCH}_2\text{CH}_2\text{OH}$, or $-\text{CH}=\text{CH}-\text{COOH}$ (R_3 and R_4 either being independently selected from the group consisting of C1-C4 alkyl, or R_3 , R_4 , and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

10 wherein E and K are independently hydrogen or hydroxyl, phosphate ester, or lower alkyl, wherein J is hydrogen or halogen.

9. The pharmaceutical composition of claim 3, wherein selective estrogen receptor modulator is OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, Lasoxifene, iproxifene, FC 1271, and GW5638.

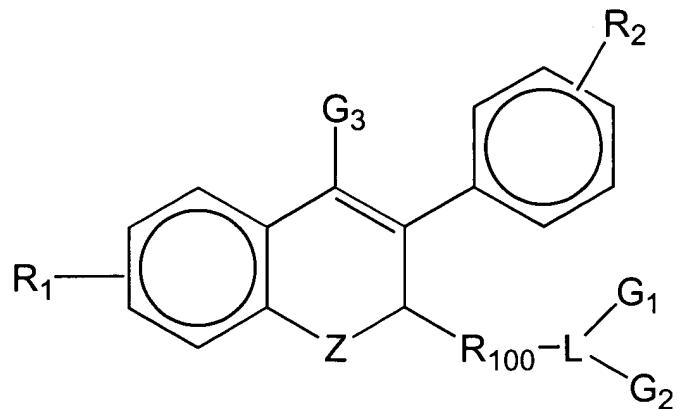
10. The pharmaceutical composition of claim 3, wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula:



5 wherein R₁ and R₂ are independently selected from the group consisting of :
hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;
wherein R₅ and R₆ are independently hydrogen or C₁-C₆ alkyl ;
wherein D is -OCH₂CH₂N(R₃)R₄ (R₃ and R₄ either being independently selected
from the group consisting of C₁-C₄ alkyl, or R₃, R₄ and the nitrogen atom to which they
10 are bound, together being a ring structure selected from the group consisting of
pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino,
hexamethyleneimino, morpholino).

11. The pharmaceutical composition of claim 10, wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

12. The pharmaceutical composition of claim 3, wherein the selective estrogen receptor modulator has the following formula:



wherein R_1 and R_2 are independently hydrogen, hydroxyl or a moiety which is
5 converted to hydroxyl in vivo;

wherein Z is either absent or selected from the group consisting of $-CH_2-$, $-O-$, $-S-$ and $-NR_3-$ (R_3 being hydrogen or lower alkyl);

wherein the R_{100} is a bivalent moiety which distances L from the B-ring by 4-10
10 intervening atoms;

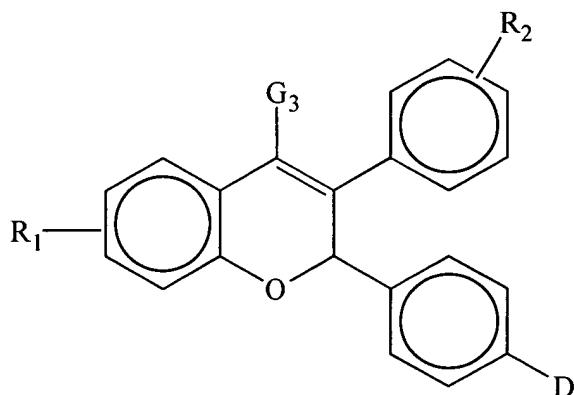
wherein L is a bivalent or trivalent moiety selected from the group of $-SO-$, $-$
CON-, $-N<$, and $-SON<$;

wherein G_1 is selected from the group consisting of hydrogen, a C_1 to C_5
hydrocarbon, a bivalent moiety which in combination with G_2 and L is a 5-to 7-
membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

15 wherein G_2 is either absent or selected from the group consisting of hydrogen, a
 C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_1 and L is a 5-to 7-
membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_3 is selected from the group consisting of hydrogen, methyl and ethyl.

13. The pharmaceutical composition of claim 12, wherein the compound is a
benzopyran derivative of the following general structure:

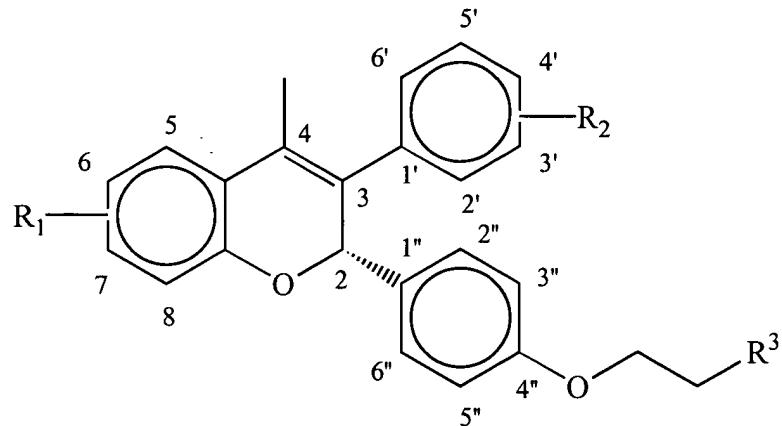


or a pharmaceutically acceptable salt thereof,

5 wherein D is $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$ (R_3 and R_4 either being independently selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, or R_3, R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino);

10 wherein R_1 and R_2 are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

14. The pharmaceutical composition of claim 13, wherein the benzopyran derivative is optically active due to a majority of its stereoisomer having an absolute configuration S on carbon 2, said compound having the molecular structure:



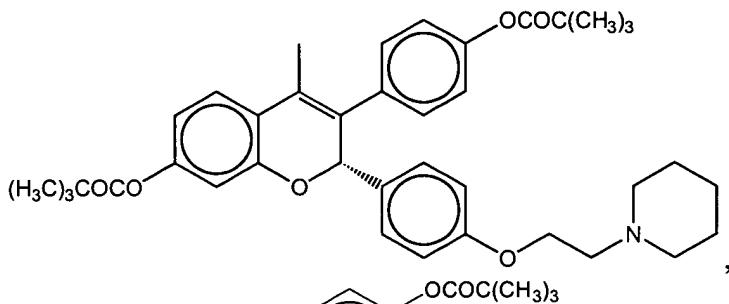
5 wherein R_1 and R_2 are independently selected from the group consisting of hydroxyl and a moiety convertible in vivo to hydroxyl;

10 wherein R^3 is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and NR_aR_b (R_a and R_b being independently hydrogen, straight or branched C_1 - C_6 alkyl, straight or branched C_2 - C_6 alkenyl, and straight or branched C_2 - C_6 alkynyl).

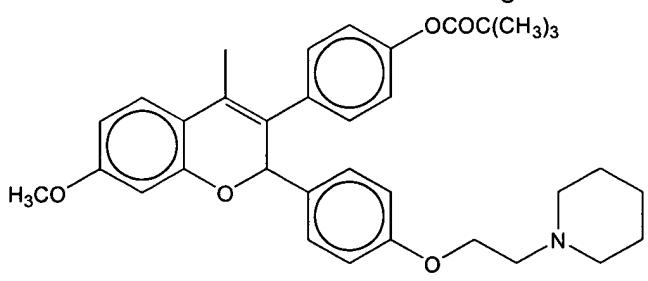
15. The pharmaceutical composition of claim 14, wherein said compound or salt substantially lacks (2R)-enantiomer.

16. The pharmaceutical composition of claim 14, wherein said selective estrogen receptor modulator is selected from the group consisting of:

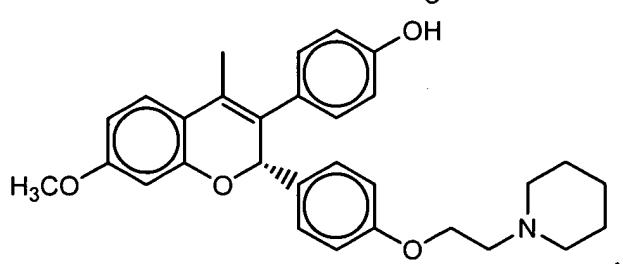
EM-800



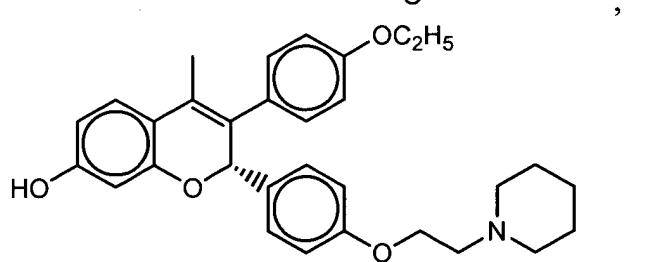
EM-1520



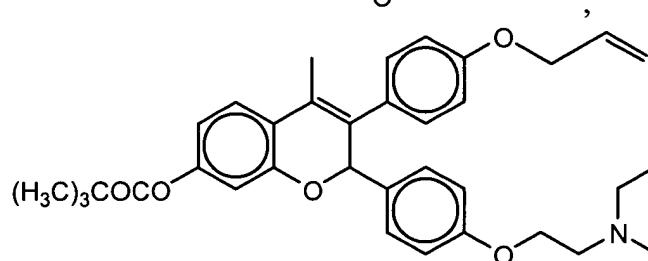
5 EM-1872



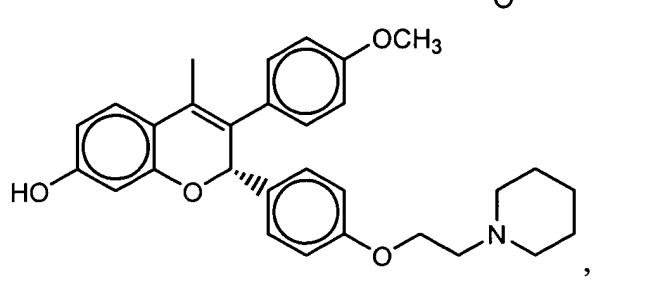
EM-1900



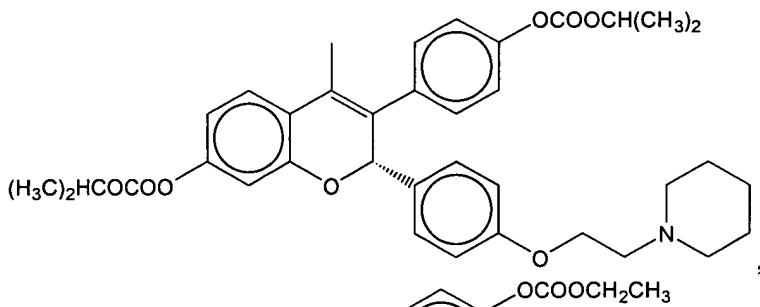
EM-1901



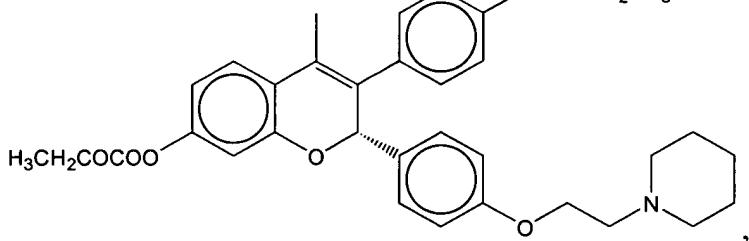
EM-1903



EM-1533

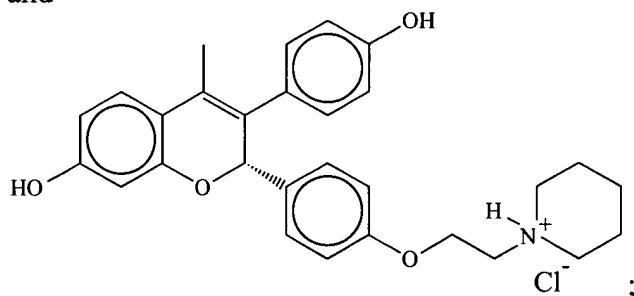


10 EM-1518



and

EM-652.HCl
(EM-1538)



15 wherein all of the foregoing molecular structures whose stereochemistry is indicated are optically active due to a majority of their stereoisomers being of 2S configuration.

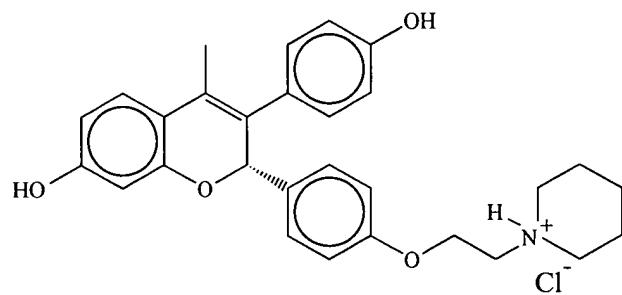
17. The pharmaceutical composition of claim 14, wherein the benzopyran derivative is a salt of an acid selected from the group consisting of acetic acid, adipic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, hydrochlorothiazide acid, 5 hydroxy-naphthoic acid, lactic acid, maleic acid, methanesulfonic acid, methylsulfuric acid, 1,5-naphthalenedisulfonic acid, nitric acid, palmitic acid, pivalic acid, phosphoric

acid, propionic acid, succinic acid, sulfuric acid, tartaric acid, terephthalic acid, p-toluenesulfonic acid, and valeric acid.

18. The pharmaceutical composition of claim 17, wherein the acid is hydrochloric acid.

19. The pharmaceutical composition of claim 1, wherein said selective estrogen receptor modulator is:

EM-652.HCl
(EM-1538)



5 and is optically active due to a majority of its stereoisomers being of 2S configuration; and

wherein the estrogen is selected from the group consisting of 17beta-estradiol, 17beta-estradiol esters, 17alpha-estradiol, 17alpha-estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 17alpha-ethynylestradiol, 10 17alpha-ethynylestradiol esters, mestranol, and mestranol esters.

20. The pharmaceutical composition of claim 1, wherein said estrogen is selected from the group consisting of 17beta-estradiol, 17beta-estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 17alpha-ethynylestradiol, 17alpha-ethynylestradiol esters, mestranol, mestranol esters, 5 chemestrogen, DES, phyttestrogen, tibolone, 2'-ethylestrogenoxazole, and ethynediol.

21. The pharmaceutical composition of claims 1, wherein said estrogen is a mixed estrogenic/androgenic compound.

22✓ A kit comprising a first container containing a pharmaceutical formulation comprising a therapeutically effective amount of at least one estrogen or a prodrug thereof; and said kit further comprising a second container containing a pharmaceutical formulation comprising a therapeutically effective amount of at least 5 one selective estrogen receptor modulator or prodrug thereof, said modulator not being a benzothiophene or a phenylindole derivative.

23✓ A kit comprising a first container containing a pharmaceutical formulation comprising a therapeutically effective amount of at least one estrogen or a prodrug thereof; and said kit further comprising a second container containing a pharmaceutical formulation comprising a therapeutically effective amount of at least 5 one selective estrogen receptor modulator or prodrug thereof, comprising at least one additional container of said kit that contains a therapeutically effective amount of at least one additional agent selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol, an androgenic agent, testosterone, 4-androstene-3,17-dione and a prodrug of any of the 10 foregoing additional agents.

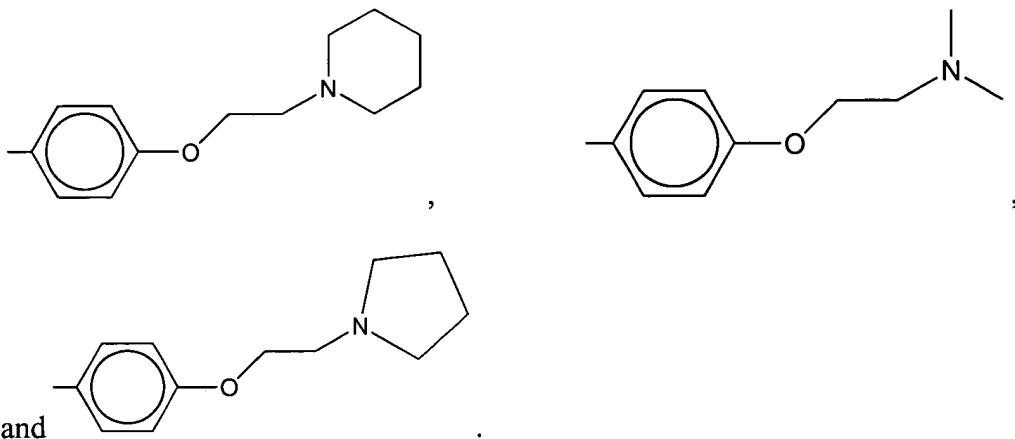
24. The kit of claim 22 further comprising at least one additional container containing a pharmaceutical formulation comprising a therapeutically effective amount of at least one bisphosphonate.

25. The kit of claims 22, wherein the selective estrogen receptor modulator has a molecular formula with the following features:

- a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or substituted by a hydroxyl group or a group converted in vivo to hydroxyl;
- 5 b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof;

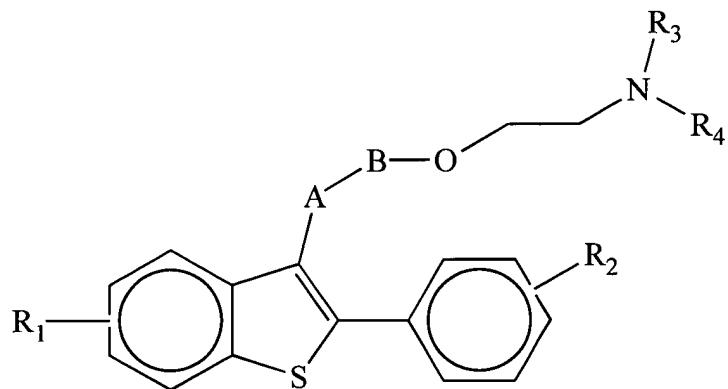
10 and wherein said modulator is not a benzothiophene derivative, a phenylindole derivative, a naphthalene derivative, an isoquinoline derivative or an enantiomeric mixture of 3-phenylquinoline derivatives, 3-pheynulthiochroman derivatives, 3-phenylchroman derivatives having more than 10% of the enantiomer of 2R configuration.

26. The kit of claim 25, wherein the side chain is selected from the group consisting of:



27. The kit of claim 25, wherein the selective estrogen receptor modulator is selected from the group consisting of a triphenylethylene derivative, benzopyran derivative, HMR 3339, HMR 3656, LY 335124, LY 326315, SH 646, ERA 923 and centchroman derivative.

28. The kit of claim 23, wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:



wherein R₁ and R₂ are independently selected from the group consisting of :

5 hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;

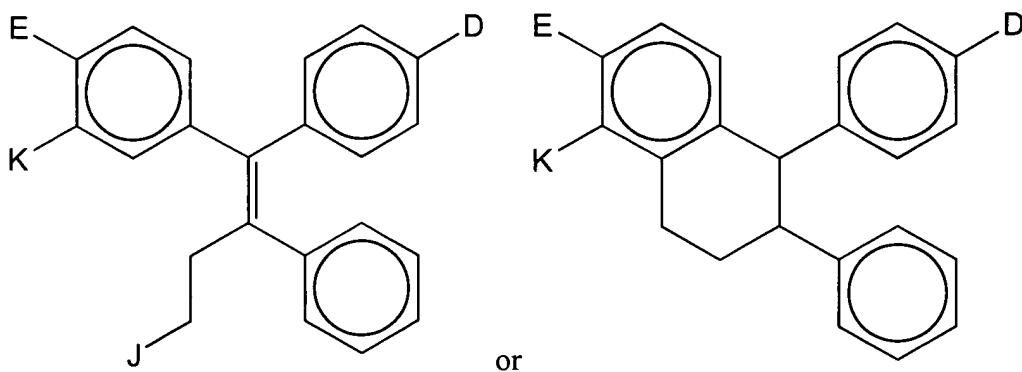
wherein R₃ and R₄ are either (a) independently C1-C4 alkyl, or (b) a moiety which in combination with the nitrogen to which they are bound, is selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;

10 wherein A is selected from the group consisting of -CO-, -CHOH, and -CH₂-;

wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC₄H₂N₂-.

29. The kit of claim 28, wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

30. The kit of claim 25, wherein the selective estrogen receptor modulator is a triphenylethylene or diphenylhydronaphthalene derivative compound of the following formula:

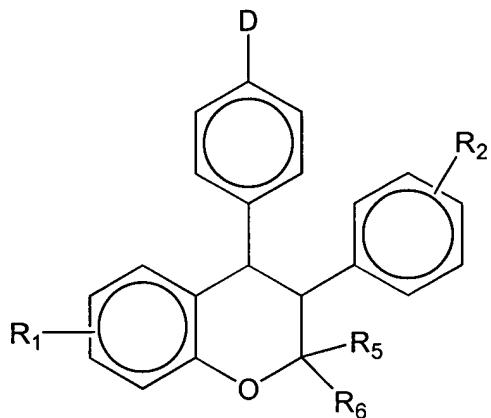


5 wherein D is $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$, $-\text{OCH}_2\text{CH}_2\text{OH}$, or $-\text{CH}=\text{CH}-\text{COOH}$ (R_3 and R_4 either being independently selected from the group consisting of C1-C4 alkyl, or R_3 , R_4 , and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

10 wherein E and K are independently hydrogen or hydroxyl, phosphate ester, or lower alkyl, wherein J is hydrogen or halogen.

31. The kit of claim 22, wherein selective estrogen receptor modulator is OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, Lasofoxifene, iproxifene, FC 1271, and GW5638.

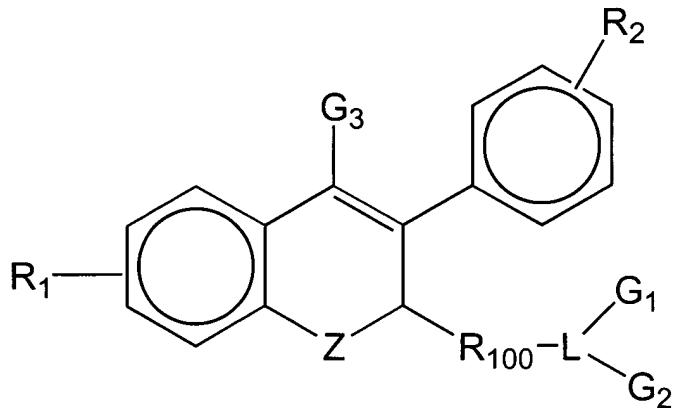
32. The kit of claim 25, wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula:



wherein R₁ and R₂ are independently selected from the group consisting of :
5 hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;
wherein R₅ and R₆ are independently hydrogen or C₁-C₆ alkyl;
wherein D is -OCH₂CH₂N(R₃)R₄ (R₃ and R₄ either being independently selected
from the group consisting of C₁-C₄ alkyl, or R₃, R₄ and the nitrogen atom to which they
are bound, together being a ring structure selected from the group consisting of
10 pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino,
hexamethyleneimino, morpholino).

33. The kit of claim 32, wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

34. The kit of claim 25, wherein the selective estrogen receptor modulator has the following formula:



wherein R₁ and R₂ are independently hydrogen, hydroxyl or a moiety which is
5 converted to hydroxyl in vivo;

wherein Z is either absent or selected from the group consisting of -CH₂-, -O-, -S- and -NR₃- (R₃ being hydrogen or lower alkyl);

wherein the R100 is a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms;

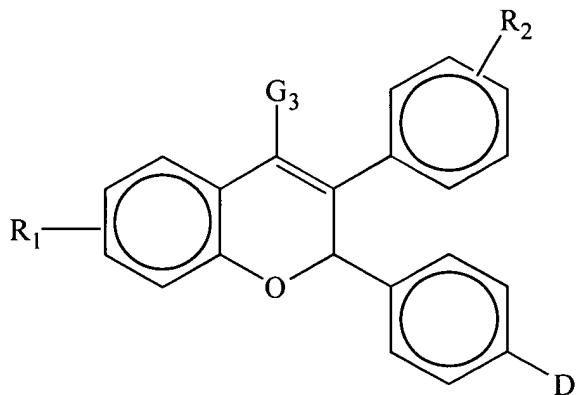
10 wherein L is a bivalent or trivalent moiety selected from the group of -SO-, -CON-, -N<, and -SON<;

wherein G₁ is selected from the group consisting of hydrogen, a C₁ to C₅ hydrocarbon, a bivalent moiety which in combination with G₂ and L is a 5-to 7-membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

15 wherein G₂ is either absent or selected from the group consisting of hydrogen, a C₁ to C₅ hydrocarbon, a bivalent moiety which in combination with G₁ and L is a 5-to 7-membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G₃ is selected from the group consisting of hydrogen, methyl and ethyl.

35. The kit of claim 34, wherein the compound is a benzopyran derivative of the following general structure:

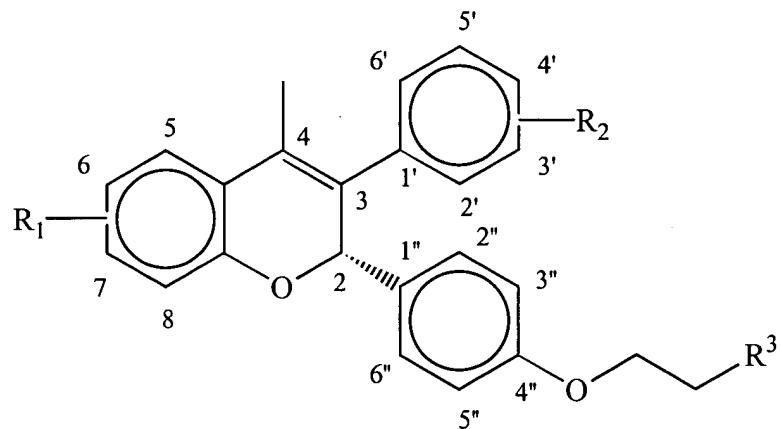


or a pharmaceutically acceptable salt thereof,

5 wherein D is $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$ (R_3 and R_4 either being independently selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, or R_3 , R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

10 wherein R_1 and R_2 are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

36. The kit of claim 35, wherein the benzopyran derivative is optically active due to a majority of its stereoisomer having an absolute configuration S on carbon 2, said compound having the molecular structure:



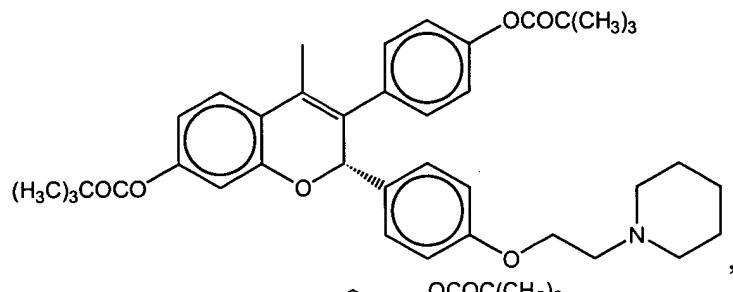
5 wherein R_1 and R_2 are independently selected from the group consisting of hydroxyl and a moiety convertible in vivo to hydroxyl;

10 wherein R^3 is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and NR_aR_b (R_a and R_b being independently hydrogen, straight or branched C_1 - C_6 alkyl, straight or branched C_2 - C_6 alkenyl, and straight or branched C_2 - C_6 alkynyl).

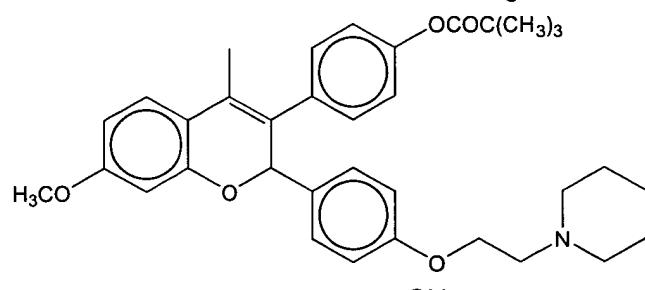
37. The kit of claim 36, wherein said compound or salt substantially lacks $\overbrace{(2R)}$ -enantiomer.

38. The kit of claim 36, wherein said selective estrogen receptor modulator is selected from the group consisting of:

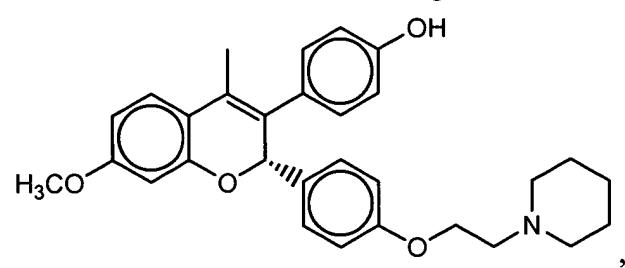
EM-800



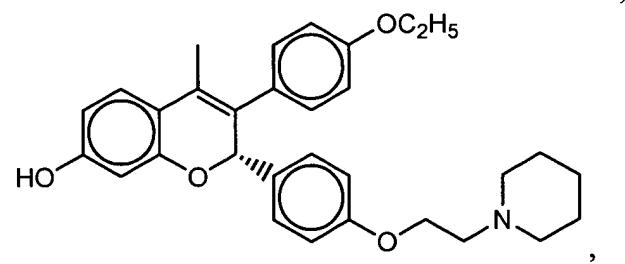
EM-1520



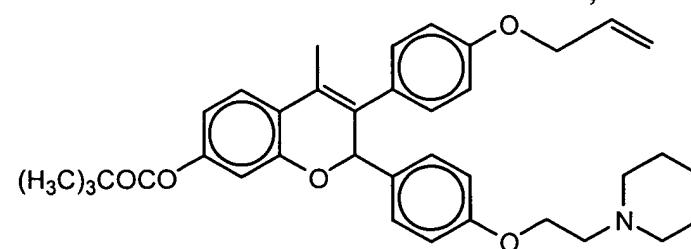
5 EM-1872



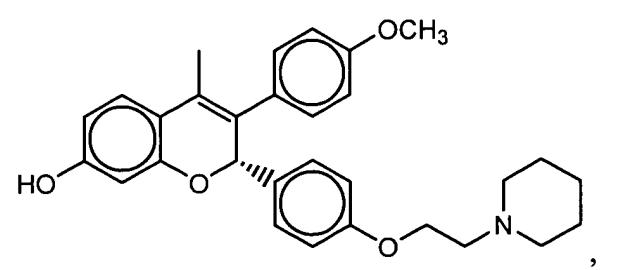
EM-1900



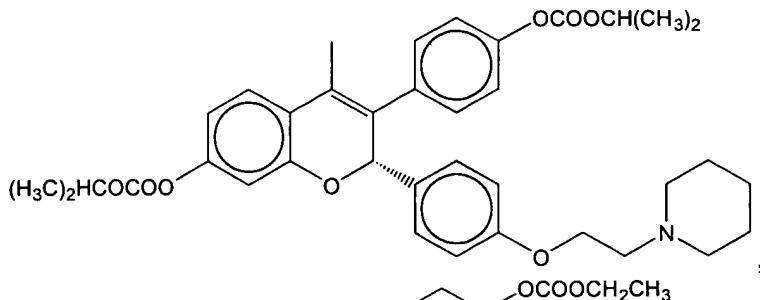
EM-1901



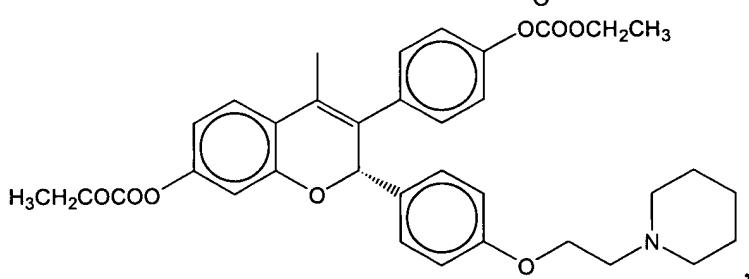
EM-1903



EM-1533



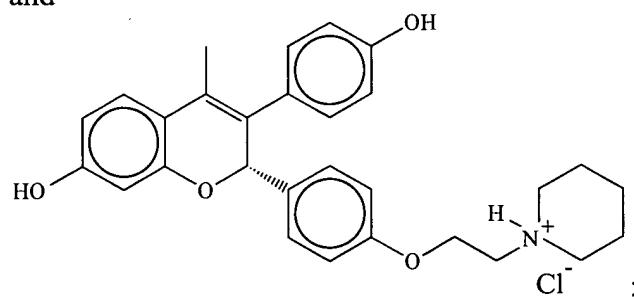
10 EM-1518



and

EM-652.HCl

(EM-1538)



wherein all of the foregoing molecular structures whose stereochemistry is indicated are optically active due to a majority of their stereoisomers being of 2S configuration.

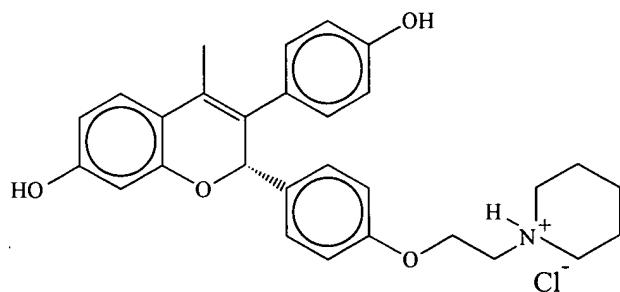
39. The kit of claim 36, wherein the benzopyran derivative is a salt of an acid selected from the group consisting of acetic acid, adipic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, hydrochlorothiazide acid, hydroxy-naphthoic acid, lactic acid, maleic acid, methanesulfonic acid, methylsulfuric acid, 1,5-naphthalenedisulfonic acid, nitric acid, palmitic acid, pivalic acid, phosphoric acid,

propionic acid, succinic acid, sulfuric acid, tartaric acid, terephthalic acid, p-toluenesulfonic acid, and valeric acid.

40. The kit of claim 39, wherein the acid is hydrochloric acid.

41. The kit of claim 22, wherein said selective estrogen receptor modulator is:

EM-652.HCl
(EM-1538)



5 and is optically active due to a majority of its stereoisomers being of 2S configuration; and

wherein the estrogen is selected from the group consisting of 17beta-estradiol, 17beta-estradiol esters, 17alpha-estradiol, 17alpha-estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 17alpha-ethynylestradiol, 10 17alpha-ethynylestradiol esters, mestranol, and mestranol esters.

42. The kit of claim 22, wherein said estrogen is selected from the group consisting of 17beta-estradiol, 17beta-estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 17alpha-ethynylestradiol, 17alpha-ethynylestradiol esters, mestranol, mestranol esters, chemestrogen, DES, 5 phyttestrogen, tibolone, 2'-ethylestrogenoxazole, and ethynediol.

43. The kit of claim 22, wherein said estrogen is a mixed estrogenic/androgenic compound.